REMARKS

After-Final Interview Requested

Applicants request an after-final interview in this application. After several unsuccessful attempts to discuss the substance of the April 2, 2008 Office Action with the Examiner (on April 21, 2008, June 17, 2008 and June 24, 2008) the undersigned spoke with SPE Frederick Krass on June 24, 2008. SPE Krass agreed with the undersigned that certain aspects of the April 2, 2008 Office Action were confusing, and that other aspects of the Office Action were lacking in detail such that advancement of prosecution would be difficult. As a result Examiner Krass stated that he would support an after-final interview in an effort to help resolve prosecution issues. To allow sufficient time for Examiner Simmons and SPE Krass to review the file, the undersigned will contact SPE Krass in 1-2 weeks to set up said interview. It is requested that no action, for instance issuance of an advisory action, be taken prior to the interview being conducted.

Status of Claims

Claims 1-17 and 35-38 are pending. Claims 18-34 have been withdrawn.

In Applicants' November 16, 2007 Response Applicants sought clarification on the Examiner's withdrawal of claim 15 from further consideration. Applicants also respectfully requested rejoinder of claim 15 (and all other claims eligible for rejoinder) upon allowance of claim 1. The April 2, 2008 Office Action is silent as to rejoinder.

Piecemeal Examination

In Applicants' November 16, 2007 Response Applicants pointed out that: The Examiner issued a new set of rejections, several of which rejections were based on the very same references as the original set of rejections. Applicants referred to MPEP 707.07(g), which states in part:

> Piecemeal examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references.

All valid and available grounds for objection / rejection were *not* presented in the first Office Action. As a result, minimal (if any) progress has been made in the substantive prosecution of this case following Applicants' November 2, 2006 paper. Applicants' rights have been unfairly prejudiced by this delay. To avoid further delay and prejudice, Applicants respectfully request that all issues remaining in this application be handled completely, and that the Examiner consider this paper promptly.

Examiner's Grounds for Rejection

Claims 1-14, 16-17 and 35-38 remain rejected under 35 USC §103 as allegedly being obvious in view of U.S. Patent 6,617,333 ("Rabindran"). Applicants traverse. Because Examiner Huynh's April 2, 2008 did not meaningfully address the substance of Applicants' response to this rejection, and in anticipation of the after-final interview discussed above, Applicants response is presented here again.

Rabindran discloses that EKB-569 may be made into oral dosage forms (e.g., tablets) with various standard excipients, including calcium carbonate. The Examiner argues that a skilled chemist would have found it obvious to vary and/or "optimize" the amount of calcium carbonate, according to the "guidance" set forth in Rabindran, in order to provide a composition with "the desired pH". This argument fails because there is no guidance whatsoever in Rabindran describing a preferred or optimal pH level, and therefore there can be no motivation to vary or optimize the amount of calcium carbonate to achieve a particular pH level.

There also is no indication in Rabindran that calcium carbonate, even if included in a tablet with EKB-569, is used for a purpose related to pH modification. Rabindran does not teach or suggest that calcium carbonate must be selected (from the list of over 25 excipients recited at column 7, lines 22-29 of Rabindran), or that a sufficient amount of this agent be used to achieve a pH of 8 or more. In fact, listed along side calcium carbonate are stearic and alginic *acids*. Thus, it is clear that Rabindran's teachings are wholly unrelated to pH values.

Applicants have carefully studied the variety of formulations containing the subject compounds, as shown in the examples and disclosure of the specification, and have made the discovery that it is necessary to form a composition with a pH of at least 8 to achieve the desired increased stability. Rabindran fails to teach or suggest this. Applicants therefore respectfully request reconsideration and withdrawal of the §103 rejection based on Rabindran.

The Examiner's comments at pages 6-7 regarding claims 7-9, claims 12-13 and claim 14 regarding additional teachings of Rabindran, do not mitigate the failures of that reference, outlined above.

Next, claims 1-14, 16-17 and 35-38 are rejected under 35 USC §103 as allegedly being obvious in view of published patent application US2004/0127470 ("Masferrer"). Again, applicants traverse. Because Examiner Huynh's April 2, 2008 did not meaningfully address the substance of Applicants' response to this rejection, and in anticipation of the after-final interview discussed above, Applicants response is presented here again.

Masferrer discloses that EKB-569 may be made into oral dosage forms (e.g., tablets) with various standard excipients, including calcium carbonate. The Examiner argues that a skilled chemist would have found it obvious to vary and/or "optimize" the amount of calcium carbonate, according to the "guidance" set forth in Masferrer, in order to provide a composition with the "desired pH". This argument fails because there is no guidance whatsoever in Masferrer describing a preferred or optimal pH level, and therefore there can be no motivation to vary or optimize the amount of calcium carbonate to achieve a particular pH level.

Moreover, there is no indication in Masferrer that calcium carbonate, even if included in a tablet with EKB-569, would be used for a purpose related to pH modification. Masferrer does not teach or suggest that calcium carbonate must be selected (from the list of excipients recited at paragraph [1209] of Masferrer), or that a sufficient amount of this agent be used to achieve a pH of 8 or more. In fact, Masferrer teaches away from a basic (high pH) oral formulation in listing the excipients phosphoric and sulfuric *acids*. Mansferrer further teaches away from a high pH oral formulation in describing calcium carbonate as a "buffer", since buffers are known in the art to *resist*, rather than cause, pH change. It is clear that Masferrer teachings are unrelated to increasing pH values, or pH values at all.

Applicants have carefully studied the variety of formulations containing the subject compounds, as shown in the examples and disclosure of the specification, and have made the discovery that it is necessary to form a composition with a pH of at least 8 to achieve the desired increased stability. Masferrer fails to teach or suggest this. Applicants therefore respectfully request reconsideration and withdrawal of the §103 rejection based on Masferrer.

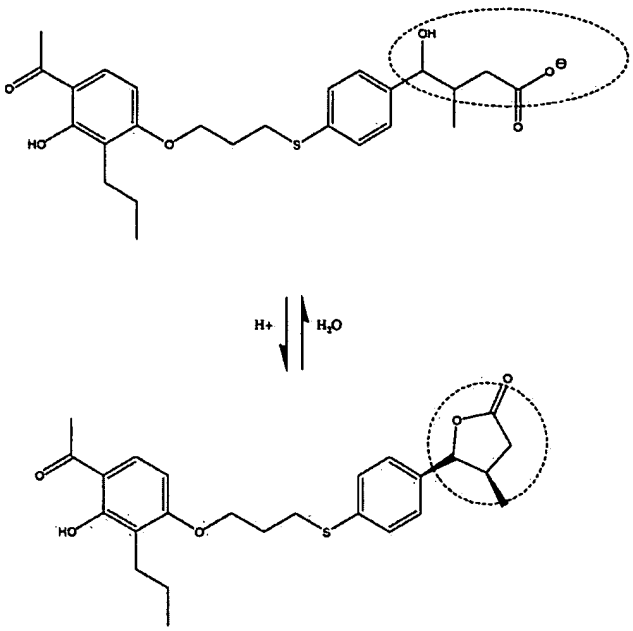
The Examiner's comments at pages 9-10 regarding claims 7-9, claims 12 and claims 35-38 regarding additional teachings of Mansferrer do not mitigate the failures of that reference, outlined above.

Claims 1-14, 16-17, and 35-38 are rejected under 35 USC §103 as being obvious over U.S. Patent 6,002,008 ("Wissner") in view of Cotton et al., International Journal of Pharmaceutics, 1994, 109, pp. 237-249 ("Cotton"). Applicants traverse. Because Examiner Huynh's April 2, 2008 did not meaningfully address the substance of Applicants' response to this rejection, and in anticipation of the after-final interview discussed above, Applicants response is presented here again.

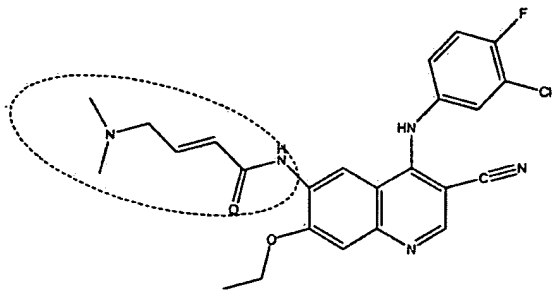
The Examiner's rejection relies on two separate logical leaps. First, the Examiner argues that Wissner's methoxy homolog of the EKB-569 is equivalent to EKB-569 itself, on the premise that homologs are known to possess "similar properties". Second, the Examiner argues that if a base can prevent degradation of Cotton's dimethylamino-but-2-enoic acid side chain, it can prevent degradation of all side chains, regardless of structural and chemical considerations. Neither of these arguments, considered separately or alone, are appropriate.

With respect to Wissner, the Examiner's conclusion that a skilled chemist "would have been motivated to prepare" the ethoxy homolog known as EKB-569 is baseless. There are any numerous of "homologs" of the Wissner methoxy compound, and the Examiner has pointed to no teaching, suggestion or motivation in Wissner for the proposition that a skilled chemist would have prepared the *particular* homolog known as EKB-569. Quite to the contrary, it is well known in the chemical arts that even small differences in chemical structure often result in profound chemical and biological differences. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006).

Cotton discloses a compound L-649,923 which includes a so-called gamma–hydroxy free acid side chain. Cotton's side chain degrades to a gamma–lactone, as shown below (emphasis added to show the side chain of interest):



Unlike the gamma–hydroxy free acid side chain of Cotton, the compound EKB-569 encompassed by the instant invention includes a structurally and chemically dissimilar dimethylamino-but-2-enoic acid side chain:



Even assuming *arguendo* that the sodium carbonate used in Cotton is responsible for preventing cyclization of the gamma–hydroxy free acid side chain of L-649,923, there is absolutely no reason a skilled chemist would conclude that sodium carbonate would also prevent cyclization of a *completely dissimilar* dimethylamino-but-2-enoic side chain. The skilled chemist would immediately recognize that the respective side chains are of different lengths, possess different heteroatoms, possess different substituents, and possess different carbon-carbon bonding patterns. In short, it would be clear that these are very different side chains, and it would not be expected that a reagent preventing cyclization of one side chain would do the same for the other.

Further, Cotton actually teaches away from the present invention in showing that the base gylcine is effective at pH levels below 8 (specifically, 7.3), and in showing that the base sodium phosphate dibasic is effective at pH levels below 8 (specifically, 7.8). It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). The alleged effectiveness of sodium carbonate at pH levels above 8 only serves to emphasize that Cotton does not teach or suggest to a skilled chemist the importance of a particular minimum pH value.

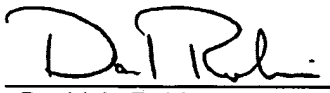
In addition to the infirmities pointed out above with respect to Wissner and Cotton considered individually, there simply is no motivation to combine these references. Wissner does not teach or suggest that there is a problem relating to degradation via side chain cyclization. A skilled chemist would have no motivation to apply any side chain stabilization technology to the Wissner compounds, or homologs thereof, in the absence of a teaching in Wissner that there is a stability problem. Thus (setting aside for the moment that Cotton's stabilization technology relates to wholly different side chain chemistry and teaches away from a particular minimum pH level, as outlined above), there would have been no motivation to apply Cotton's stabilization technology to Wissner. (The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432.)

It is clear that the Examiner is impermissibly employing hindsight reasoning to establish a motivation to combine Wissner and Cotton. Specifically, the Office Action at page 11, lines 14-17, refers to the instant application's disclosure at page 14 to establish that "the basic excipient ...is used to stabilize and prevent the degradation of the pharmaceutical composition caused by cyclization...". Other than this improper reference to the present application, the Examiner has pointed to no motivation to combine Wissner and Cotton.

The Examiner's comments at pages 13-14 regarding claims 7-9, claims 12 and claims 35-38 regarding additional teachings of Wissner and/or Cotton do not mitigate the failures of those references, outlined above.

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of all pending rejections, and prompt issuance of a Notice of Allowance.

If any issues remain after consideration of this Amendment, the Examiner is urged to contact the undersigned by telephone at 845-602-4760.



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